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10/510,015	04/18/2006	Claudio Soto-Jara	ARS-102	4494

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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,015	SOTO-JARA ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *95-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *95-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2008 has been entered.

Status of the claims

2. In the amendment submitted on 10/29/2008 Applicant has canceled claims 35 - 37, 39 and 57-94 and added new claims 95-138, which are now pending.

Claim Objections

3. Claim 97 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Specifically, the dependent claim 97 is worded as "further comprising a molecule..." while the independent claim 95 is drawn to "an isolated peptide consisting of".

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 95-97, 100, 104, 106, 107, 109, 110, 111, 113-114, 120, 121,123, 124 126-127, 133, 134, 136, and 138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the independent claims 95, 111 and 124 contain the recitation: An isolated polypeptide consisting of:

f) a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:

- ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
- iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;

It is unclear if the words "said polypeptide" refers to the polypeptide consisting of a fusion polypeptide or a peptide comprising a protein sequence other than human OX 40L or to the fusion polypeptide or to the isolated polypeptide. Thus, the metes and bounds of the claims could not be determined. The claims 96-97, 100, 104, 106, 107, 109, 110, 113-114, 120, 123, 124, 126-127, 133, 134, 136, and 138 are rejected as being dependent claims.

In addition, the wording "wherein said polypeptide consists of between 5 and 10 contiguous amino acids of between 5 and 10 contiguous amino acids of SEQ ID NO: 1," in claims 100,114, 127 render the claims unclear, hence the metes and bounds of the claims could not be determined.

Also, claim 104 recites: "fused to a peptide consisting of amino acids 94-124 of human OX40L" is indefinite because there is no SEQ ID NO attached to the peptide and the numbering of amino acids is not intrinsic to the polypeptide. As such, the metes and bounds of the claims could not be determined.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The claim is drawn to an isolated peptide that consists of specific sequences from the human OX40L that are acetylated, carboxylated or PEGylated. The specification does not disclose that the peptide is PEGylated.

7. Claims 95-97, 99-100, 102-104, 106-111, 113-114, 116-118, 120-124, 126-127, 129-130 and 133 -138 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated peptides, compositions containing them, comprising SEQ ID NOs: 6 and 8 does not reasonably provide enablement for SEQ ID NO: 13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to isolated polypeptides or compositions comprising isolated polypeptides consisting of SEQ ID NOs: 6, 8 and 13 as well as mutants, derivatives, mimetics (peptide or non-peptide) of them. The claims are interpreted such as the polypeptides having as a crucial functional property (as needed for fulfillment of the utility requirement) the property of binding to the OX40R). As such, the prior art is aware of polypeptides containing the sequences 6, 8 and 13 (Godfrey et al. (U.S. Pat. 6,242,566 -cited in the prior Office actions). What is not anticipated is that the SEQ ID

NOs: 6, 8, and 13 are the actual binding regions. In the art there are methods of finding protein-protein interaction binding domains. The predictability is in a direct relationship with the size of the domain (i.e. the higher the number of the amino acids in the domain, the higher the probability that the domain contains the actual binding surface). Once the number of amino acids in the binding domain is narrowed, it becomes less and less predictable if the peptide is an actual binding interface or not and reduction to practice is needed. The specification presents in Example 2 a screening assay for detecting of binding properties of polypeptides having between 10-31 amino acids that include the peptides of SEQ ID NOs: 6 and 8. The results are presented in Figures 5 and 6. The SEQ ID NO: 13 is a 5mer and it was not actually tested. It is just inferred that it must be a binding domain based on a series of indirect experiments. There is no guidance, but in the best case scenario a hypothesis that he SEQ ID NO: 13 is an actual binding region. In a Table attached to the Remarks submitted on 10/29/2008, the Applicants' representative tried to allege that SEQ ID NO: 13 actually binds to OX40R and inhibits its interaction with OX40L. The last line in the Table has no factual basis in the Application. At any rate, the specification does not present any working example to support the allegation that the SEQ ID NO: 13 is a *bona fide* binding domain. This would leave a person of ordinary skill in the art in the burdensome situation of testing the sequence mentioned with a high level of unpredictability since the sequence is relatively short and it is hard to establish if such a short binding region is necessary and sufficient to bind to OX40R and inhibit the binding of the OX40L *per se*.

Due to the large quantity of experimentation necessary to detect actual binding domains of peptides shorter than 10 amino acids; the absence of working examples directed to same; the state of the prior art which establishes the unpredictability of the binding once the number of amino acids is shortened under 10 amino acids, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 95-136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. 6,242,566 -cited in the prior Office action) in view of Chien et al. (Proc. Natl. Acad. Sci. USA, 88, 9578-9582, 1991-cited in the prior Office action), and Hamaoui et al. (J. Parenter. Enter. Nutr. 14, 501-507, 1990). .

The claims are drawn to an isolated polypeptide consisting of:

a) SEQ ID NO: 6;

b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);

c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;

d) SEQ ID NO: 8 or SEQ ID NO: 13; e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;

f) a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:

i) SEQ ID NO: 6;

ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);

iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R; or

iv) SEQ ID NO: 8 or SEQ ID NO: 13; or

g) a derivative of a), b), c), d), e) or f).

Also claimed is a composition comprising the peptide and a pharmaceutically acceptable carrier or a composition of matter comprising the polypeptide and a solid support.

In the Application, the SEQ ID NO: 6 represents 31 amino acids (amino acids 94-124 of the human OX40L) and comprises the SEQ ID NO: 8 (amino acids 107-116) which in turn comprises the SEQ ID NO: 13 (amino acids 107-111).

Godfrey et al. teach purified ACT-4-L (which is an earlier name for OX40L- as acknowledged by Applicant) ligand polypeptides; an exemplified ACT-4-L ligand designated ACT-4-L-h-1. The polypeptide of Seq. Id. No.: 6 of the instant Application is 100% identical with the amino acid string 94-124 of the Seq. Id. No.: 4 of Godfrey et al. (result presented in the prior non-final Office action). Godfrey et al. also teach purified extracellular domains of ACT-4-L ligands the sequence 51-183 of the OX40L is presented as being the extracellular region of the protein and, by inference, the portion of the polypeptide implicated in the binding to the OX 40- its receptor. The purified

extracellular domains taught by Godfrey et al. comprise at least five contiguous amino acids from the full-length ACT-4-L-h-1 extracellular domain. ACT-4-L ligand polypeptides are also useful as agonists or antagonists of an ACT-4 receptor, and can be used in the therapeutic methods. Some extracellular domains consist essentially of a domain possessing a particular functional property, for example, the capacity to specifically bind to the ACT-4-h-1 receptor expressed on the surface of $CD4^+$ T-cells. Any of the above extracellular domains may further comprise a linked second polypeptide such as the constant region of an immunoglobulin heavy chain (col. 2, line 46 to col. 3, line 5). Also described by Godfrey et al. are ligands representing allelic, nonallelic, splice and higher cognate variants of ACT-4-L-h-1, and natural or induced mutants of any of these. Such variants will typically show substantial sequence identity with the ACT-4-L-h-1 sequence, and contain at least 4 and more commonly 5, 6, 7, 10 or 20, 50 or more contiguous amino acids from the ACT-4-L-h-1 sequence (col. 12, lines 15-22). Besides the full-length polypeptides, Godfrey et al. teach biologically active fragments of full-length ACT-4-L ligand polypeptides (synonymous to active mutant of the instant application). Significant biological activities include binding to an ACT-4 receptor such as ACT-4-h-1 and a segment of a full-length ACT-4-L ligand polypeptide will ordinarily comprise at least 5 contiguous amino acids of the ACT-4-L (col.13, lines 21-38). Godfrey et al. also disclose fusion partners for the ACT-4-L polypeptides that include toxins (e.g., diphtheria toxin, Pseudomonas ectotoxin A, ricin toxin or phospholipase C) and immunoglobulin components. The recombinant globulins formed by fusion of ACT-4-L fragments and immunoglobulin components often have most or all

of the physiological properties associated with the constant region of the particular immunoglobulin class used (col. 14, lines 58-59, col. 10, lines 43-53). The fusion proteins can be used to immobilize the peptide by the way of recombinant globulins, for binding analysis (i.e., solid support) (col. 11, lines 1-3; col.14, lines 64-67; col. 23, lines 1-3). Godfrey et al. also teach that ACT-4-L polypeptides can be synthesized by chemical methods which are well known in the art and necessarily include a solid support for the synthesis of the peptide and are described further by Berger & Kimmel, Methods in Enzymology, Volume 152, Guide to Molecular Cloning Techniques Academic Press, Inc., San Diego, Calif., 1987) (col. 16, lines 35-42).

Godfrey et al. also teach pharmaceutical compositions containing fragments of the ACT-4-L and suitable pharmaceutical excipients, carrier, stabilizers, etc (col. 24, line 63 to col. 24 line13).

Godfrey is silent with respect to the specific sequences (by amino acid positions) that contain the specific domains involved in the specific binding to OX 40 R. It is noted though that once these specific amino acids were identified, it was routine in the art to introduce conservative mutations or delete non essential amino acids and retain the functionality of the domain. This approach is known in the art and applies for instance in the detection of a binding domain in a specie and predicting the binding domain in another specie based on the homology between the respective peptides as exemplified with the mouse derived peptide P-OX-1 (Stuber E and Strober W, J Exp Med, 183: 979-989, 1996- cited in the Specification).

Chien et al teach a method by which a protein-protein interaction is identified in vivo through reconstitution of the activity of a transcriptional activator. The method is based on the properties of the yeast GAL4 protein, which consists of separable domains responsible for DNA-binding and transcriptional activation Plasmids encoding two hybrid proteins, one consisting of the GAL4DNA-binding domain fused to protein X and the other consisting of the GAL4 activation domain fused to protein Y, are constructed and introduced into yeast. Interaction between proteins X and Y leads to the transcriptional activation of a reporter gene containing a binding site for GAL4. The utility of this in vivo approach (designated the two-hybrid system) to screen a random library for an interacting protein is presented and the authors also underscore the obviousness of the method for identifying interacting peptides (Introduction, second paragraph).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the methodology of Chien et al. to detect the interacting domains of the ACT-4-L to its receptor with a reasonable expectation of success because the methods used were readily available (as taught by Chien et al., which also suggested the usefulness of the method). The motivation to do so is offered by Godfrey et al. which teaches the uses of the ACT 4 L fragments and their biological use. By employing the methods of Chien et al. a person of ordinary skill in the art would have necessarily arrived to the domains that are essential to the binding of ACT 4 L (i.e., OX 40L) to its receptor because the domain to be searched was disclosed by Godfrey et al. (51-183 of the OX40L) so that the search would have entailed a finite number of fragments, already envisioned (in length) perfectly feasible within the technical grasp of

a person of ordinary skill in the art which read the references as a whole. On page 14 of the Remarks Applicant argues that it was unknown "whether OX40L interacts with its cognate receptor via a linear peptide or via a conformational arrangement of the homotrimer and the cited combination of references provides no teaching as to why one of skill in the art, in view of such a recognition, would have had a reasonable expectation of identifying linear peptides having the ability to bind to OX40R and antagonize its activity."

. The arguments were carefully considered but not found persuasive because the Chien method would have responded to the supposed conundrum mentioned above by Applicant, since the method of two-hybrid system would easily identify a binding motif with relatively easiness.

12. Claim 137 is rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. 6,242,566 -cited in the prior Office action) in view of Chien et al. (Proc. Natl. Acad. Sci. USA, 88, 9578-9582, 1991-cited in the prior Office action), and Hruby et al. (Curr. Med. Chem. 7,945-970, 2000- cited in the Application).

The claim is drawn to an isolated peptide, peptide mimetic, or a non-peptide mimetic of SEQ ID NO: 8 or SEQ ID NO: 13.

The teachings of Godfrey et al. and Chien et al. were presented above. They were silent about peptidomimetics.

Hruby et al. teach the design of peptidomimetic ligands with agonist biological activities. The motivation for this is that although native biologically active peptides have

a great potential for medical applications, they often need to be modified to overcome certain problems inherent in current drug-delivery strategies. The properties desired but often not present or optimized in the native ligand include: receptor/acceptor selectivity; high potency; stability against proteolytic breakdown; and appropriate biodistribution and bioavailability. These issues have been addressed by the design of peptidomimetics. A peptidomimetic is a designed compound whose pharmacophoric stereostructural elements mimics a peptide's pharmacophoric elements in 3D space, and which mimic the binding, the biological agonist (or antagonist) activity, and the structure-activity relationships of a natural endogenous peptide ligand or peptide ligand with equivalent or superior bioactivity (abstract and p. 946).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made, once the binding domain of the OX40R binding peptide are determined as taught by the combinations of teaching of Godfrey et al., Chien et al. and Hamaoui et al., to design peptidomimetics based on the teachings of Hruby et al. with a reasonable expectation of success. The motivation is underscored in Hruby et al. to obtain superior therapeutic compounds.

Claim 138 is rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. 6,242,566 -cited in the prior Office action) in view of Chien et al. (Proc. Natl. Acad. Sci. USA, 88, 9578-9582, 1991-cited in the prior Office action) and Quillan et al. (U.S. Pat. No. 6,602,856).

The claim is draw to the isolated polypeptide of the independent claim (see *supra*), wherein said polypeptide is acetylated, carboxylated or PEGylated.

The teachings of Godfrey et al. and Chien et al. were presented above. They were silent about acetylation or carboxylation of the peptide.

Quillan et al. teaches peptide antagonists of α-melanocyte stimulating hormone (abstract). The peptides can be derivatized by blocking groups, including but not limited to, acetylation, or carboxylation at the amino-terminus and amidation at the carboxy-terminus to provide protected derivatives (col. 6, lines 16-20) so as they are not degraded by exopeptidases.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have obtained peptides constituting the binding domain of the OX40R binding peptide are determined as taught by the combinations of teaching of Godfrey et al. and Chien et al. and to protect them based on the teachings of Quillan et al. with a reasonable expectation of success. The motivation is present in the Quillan et al. patent and presented above.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is

(571)272-9941. The examiner can normally be reached on 8:30-18:00 M-Th and 8:30-18:00 alternative F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/

Primary Examiner, Art Unit 1647